Development of new glucocorticosteroids with a very high ratio between topical and systemic activities

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Abstract: The very potent topical anti-inflammatory glucocorticosteroids (GCS) most widely used are either 17α-esters of halogenated 16-methyl-17α-hydroxy-corticosteroids (e.g. beclomethasone 17α,21-dipropionate = BDP) or 16α,17α-acetals of halogenated 16α,17α-dihydroxy corticosteroids (e.g. triamcinolone acetonide = TA).

The purpose of the present investigation was to increase the ratio between the topical anti-inflammatory (TAIP) and the systemic potencies (SP) of GCS 16α,17α-acetals, as such compounds are not biotransformed in the lung. Structure-activity investigations in rodents showed that fluoro substituents in positions 6α or 9α or both 6α, 9α increased SP more than TAIP. On the other hand, nonsymmetrical 16α,17α-acetal substitution increased TAIP more than SP. The best TAIP:SP ratio was obtained with budesonide, which contains this new type of acetal substituent, but has no halogen atoms in the steroid nucleus. In the rat and the mouse budesonide has a 5–10 times better TAIP:SP ratio than 16α,17α-acetonides, like TA, as well as 17α-ester GCS, like BDP. The improved ratio for budesonide is probably due to a high intrinsic GCS activity at the site of application combined with an effective inactivation by biotransformation after systemic absorption. The importance of the inactivation in the liver was verified by experiments in which the biotransformation capacity of the liver was blocked by SKF-525 A.

Key words: glucocorticosteroids – topical potency – systemic potency – anti-inflammatory – structure-activity relationship – drug metabolism – liver.

Glucocorticosteroids (GCS) effectively relieve the symptoms of severe asthma via mechanisms that are still only partly understood (25). The effects are probably mediated via the GCS-receptors (9). The GCS-receptors are considered to be very similar in the entire body (6). This would explain why in oral therapy it has not been possible to differentiate the desired anti-asthmatic action in the lung from other types of GCS-activity.

The structural elements currently considered necessary for inducing GCS-actions are shown in Figure 1. By modifications of the hydrocortisone molecule in the positions 1, 2, 6, 9, 16 or 17 it was possible already in the fifties and sixties to develop hormones with enhanced GCS- but with reduced mineralocorticoid activities. Examples of such improved GCS for oral systemic therapy are prednisolone (non-halogenated) or triamcinolone, dexamethasone and betamethasone (all 9α-halogenated). The structure of triamcinolone is given in Figure 2. However, these potent GCS have poor topical GCS effect. By masking some of the hydroxy
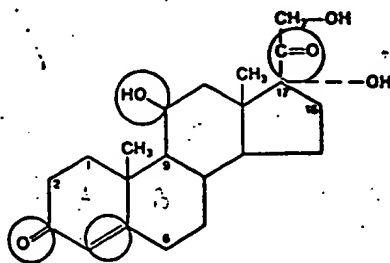
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Figure 1.
Structural formula of hydrocortisone with the groups essential to anti-inflammatory activity encircled.

substituents with ester or acetonide groups it was possible to transform the above mentioned halogenated compounds into derivatives with high topical activity (for reviews of GCS development see ref 19, 20). The structures of two such derivatives are shown in Figure 3. The development of GCS with a strong topical anti-inflammatory effect has proved of great importance in dermatological therapy.

It took nearly two decades before the unique benefits of GCS in asthma could be exploited by inhalation therapy. Early trials resulted either in no anti-asthmatic activity (e.g. hydrocortisone. prednisolone) or in the same general hormonal actions as in oral therapy (e.g. dexamethasone esters — for review see ref 14). The first known GCS to possess the desired 'topical' GCS action in the lung combined with only relatively little systemic GCS activity were the 17α-ester compounds beclomethasone 17α,21-dipropionate (BDP — Fig 3) and betamethasone 17-valerate (10, 14). Later on, a similar differentiation between the 'topical' and the systemic activity was demonstrated (7) also for 16α, 17α-acetonide GCS, e.g. triamcinolone acetonide (Fig 3) and flunisolide. These GCS were originally developed for topical dermatological therapy. The potencies found in screening models intended for evaluation of the topical cutaneous anti-inflammatory activity thus seemed to be a rather good prediction also of the anti-asthmatic activity on inhalation (10).
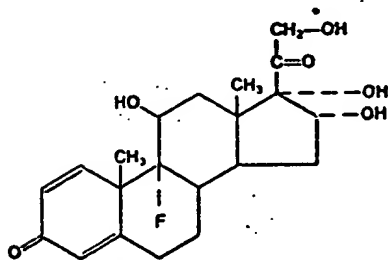

Figure 2.
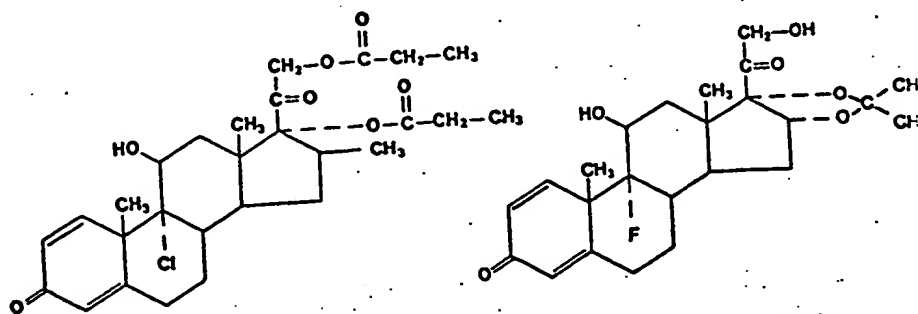*Structural formula of triamcinolone.*

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Figure 3.
Structural formulas of (a) beclomethasone 17α,21-dipropionate and (b) triamcinolone acetonide.

What properties are, then, necessary for securing the desired differentiation between the 'topical' activity in the lung and the systemic hormonal activity? Suitable candidates must have a high intrinsic GCS potency, as they are greatly diluted in the lung. This probably explains why hydrocortisone and prednisolone have not demonstrated any significant 'topical' activity when inhaled. The next requirement is a low systemic activity. Hitherto it has not been possible to differentiate between the desired and the undesired types of GCS activity at the receptor level. An alternative way to reduce the undesired systemic activities is to modify the GCS molecule so that it will be rapidly inactivated by biotransformation. This is a plausible explanation for the relatively low systemic activity of BDP (10). The topical potency of the intact 17α,21-diester is reportedly high, but it is reduced after hydrolysis of the 21-propionate group and very markedly diminished after hydrolytic cleavage also of the 17-ester bond (10). The first step occurs to a great extent already in the lung, resulting in some loss of local activity. Are the currently used halogenated topical GCS (16-methyl-17α-hydroxy-substituted pregnadienes, such as BDP, and 16α, 17α-dihydroxy substituted pregnadienes such as TA (cf. Fig 3) the best available for inhalation therapy, or can the differentiation between the 'topical' and the systemic activity be improved still more? To find an answer to this question we undertook structure-activity investigations on the importance of 1) the steroid nucleus halogenation and 2) modifications in the hitherto used 16α,17α-acetonide substitution. The original observation that introduction of steroid nucleus halogens enhanced the GCS activity was made in models (e.g. the liver glycogen deposition test and the cotton pellet test), where the test compounds were given by systemic routes (23, 24). The potent systemic GCS thus obtained (e.g. betamethasone and triamcinolone) were converted to topically highly active drugs by introduction of lipophilic substituents in the 16-and/or 17-positions (19, 20). However, as far as we know it has not been systematically documented and reported whether the steroid nucleus halogenation is equally important for the topical as for the systemic potency of GCS. We therefore undertook a further investigation in which topical test models were used. Our interest was focused on 16α,17α-acetal GCS as it was thought that such compounds would not be biotransformed locally in the lung. Accordingly, no

decrease in their local anti-asthmatic activity would be expected in the target organ.

MATERIALS AND METHODS

Glucocorticosteroids

The structures and generic names of the 16α, 17α-acetal GCS tested are shown in Table 1. Two types of acetals were prepared and compared, the currently used symmetric 16α, 17α-acetonides (named acetal type A) and a new non-symmetric 16α,17α-acetal (type B) (5, 26). The 6α-fluoro substituted acetal B compound was not available.
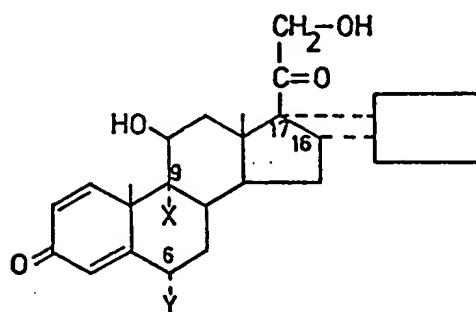
Animals

The animal experiments were performed on young male Sprague Dawley rats weighing 90–100 g or on male NMRI-mice weighing 20–25 g.

Human volunteers

Tests to determine the topical skin blanching potency of GCS were performed on the volar side of the arms.

Table 1.
Structures and generic names of the 16α,17α-acetal glucocorticoids investigated.

Fluoro substitution		Acetal substituent in 16α,17α-positions	
		Type A	Type B
X	Y		
H	H	Prednacinolone acetonide	Budesonide
H	F	Flunisolide	–
F	H	Triamcinolone acetonide	S-1298
F	F	Fluocinolone acetonide	S-1314

There are no known reliable models for testing the 'topical' anti-inflammatory potency in the lung, for which reason the topical or the local potency was assessed in other sites.

The topical anti-inflammatory activity was tested as the potency to inhibit ear edema formation in rat or mouse ears in a model (4) similar to the 'Tonelli test' (27). The GCS were applied topically as acetone solutions (20 µl/ear side in rats and 10 µl/ear side in mice) 16 h before edema induction. In this test the GCS's ability to inhibit formation of an acute and localized edema was judged (for details see ref 4). The topical 'blanching' potency was determined after application of ethanol solutions of the GCS on human skin as described by Gruvstad and Bengtsson (8).

The local anti-granuloma potency was tested in a cotton pellet model in rat (26), which reflects the GCS ability to counteract inflammation by blocking cell infiltration, multiplication and connective tissue formation. The test substances were deposited in the cotton pellets to enable assessment of their local anti-inflammatory activity. Results from this model are not given in the present publication but they have been in good accordance (26, and in the files of Draco) with the results obtained in the two topical models.
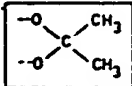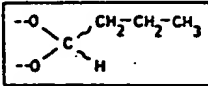
Tests for systemic GCS potency

In rats and mice the systemic effect of GCS is most easily and accurately assessed from the extent of thymus involution 4 days (rats) and 3 days (mice) after application of the drugs. The systemic potency was determined in these two species after topical, oral and subcutaneous application (for details see ref 4).

Inhibition of liver biotransformation capacity

To study the influence of liver biotransformation capacity on the systemic potency of budesonide, male rats were pretreated with either saline or SKF-525 A, 50 mg/kg by i.p. injection. This dose of SKF-525 A is reported to markedly inhibit

Table 2.
Topical anti-inflammatory activity determined in the rat ear edema model. The activity is expressed as relative potency in relation to budesonide. Structures and generic names appear from Table 1. At least 4 doses of each corticoid were tested with 12 ears/dose.

Fluoro substitution		Acetal substituent in 16a,17a-positions	
X	Y	Type A	Type B
H	H	0.2	1 (= budesonide)
H	F	0.7	-
F	H	0.3	2.2
F	F	0.7	2.5

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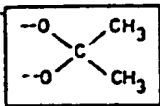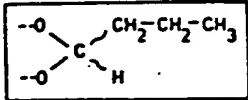
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H	H	0.2	1 (= budesonide)
H	F	0.7	–
F	H	0.3	2.2
F	F	0.7	2.5

the activity of mixed function oxidases in the liver (12). Thirty min after the pretreatment, budesonide was given to the two groups by the topical (epicutaneous), oral, intratracheal or subcutaneous route. The ability of budesonide to cause involution of the thymus in the saline and in SKF-525 A treated groups was compared.

Statistics

Dose-response investigations of all the parameters studied were performed with at least 4 doses, on a logarithmic scale. The relative potencies of the GCS tested were calculated by linear regression analysis (13) in relation to the non-halogenated acetal type B compound budesonide (potency = 1) (4).

RESULTS

Topical anti-inflammatory potency in rats and in human volunteers

The ability of 16α,17α-acetal GCS to inhibit ear edema in rats is clear from Table 2. The results show that it is more important to change the type of acetal substituent (A to B) than to introduce one or two fluorine atoms into the steroid ring skeleton to secure high topical anti-inflammatory potency.

In the induction of skin blanching the acetal B compounds were at least 5 times more potent than the corresponding derivatives of type A (Table 3). Introduction of fluoro substituents enhanced the topical potencies only 2-3 times in type B acetals and somewhat more in type A derivatives. Budesonide (type B and non-fluorinated) had about double the topical potency of fluocinolone acetonide (type A and 6α, 9α-difluorinated).

Systemic glucocorticoid potency in rats

By increasing the topical doses it was possible to induce also systemic effects. The acetals of type B had the same or even lower systemic potencies than the corresponding GCS of type A (Table 4). Fluorination greatly enhanced the

Table 3.
Topical GCS activity in the skin "blanching" model. For explanations, see Tables 1 and 2. Five doses of each GCS were tested in each of 10–20 volunteers.
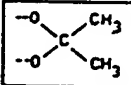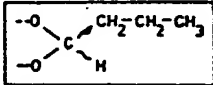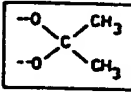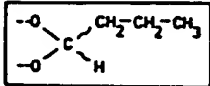
Fluoro substitution		Acetal substituent in 16α,17α-positions	
X	Y	Type A	Type B
H	H	0.1	1 (= budesonide)
H	F	0.4	–
F	H	0.4	2.2
F	F	0.6	2.8

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Table 6.

Ratio between the relative potencies for inhibition of ear edema formation (Table 2) and thymus involution (Table 4) after topical application to rats.

Fluoro substitution		Acetal substituent in 16α,17α-positions	
X	Y	Type A	Type B
H	H	0.11	1 (= budesonide)
H	F	0.05	–
F	H	0.05	0.88
F	F	0.08	0.46

Topical selectivity of budesonide in relation to beclomethasone 17α,21-dipropionate (BDP)

The improved selectivity reached with budesonide would be of clinical interest, if it was also better than that of the currently best 16-methyl-17α-hydroxy GCS, e g BDP. The topical selectivities of budesonide and BDP have been compared with similar methods, described above, but in mice since BDP had no topical anti-inflammatory effect in rats (results in rats not shown). Then, the ability of BDP to inhibit ear edema formation was about half of that of budesonide (Table 7). This is consistent with the topical 'blanching potency' in man (11). The ability to cause involution of the thymus after topical (Table 7) or oral (results not shown) application in mice was, however, 3–4 times greater for BDP than for budesonide. Thus, budesonide attained also a 5 to 10-fold better ratio between the topical and systemic activities than BDP (Table 7).

Importance of liver biotransformation rate for the systemic potency of budesonide

In rats pretreated with SKF-525 A, which blocks the mixed function oxidases of the liver, budesonide was about 5 times more potent to cause involution of the

Table 7.

Relative potencies of budesonide and beclomethasone 17α,21-dipropionate to inhibit ear edema formation and thymus involution after topical application to mice. At least 4 doses of each compound were tested in at least 3 animals/dose.

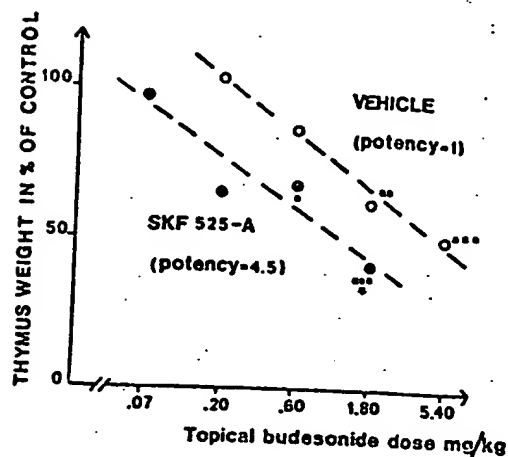| Compound	Topical anti-inflammatory potency	Systemic potency	Ratio between the topical and systemic potencies
Budesonide	1	1	1
Beclomethasone-17α, 21-dipropionate	0.4	3.5	0.1

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Figure 4.

Effect of SKF-525 A or vehicle (saline) on the systemic potency of budesonide. N = 4/dose.

a,aa,aaa = p < 0.05, 0.01 resp 0.001 compared to control

★ = p < 0.05 compared to vehicle

thymus than it was in saline-pretreated animals (Fig 4). Similar results, verifying the hypothesis of a rapid inactivation of budesonide in the liver under normal conditions, were obtained also after oral, intratracheal and subcutaneous administration of budesonide (results not shown).

.DISCUSSION

In steroid inhalation therapy in asthma and rhinitis 'topical' anti-anaphylactic and anti-inflammatory effect on the airways is desired (17, 18). This requires a high intrinsic GCS activity as the compounds are markedly diluted at least in the lungs. To increase the activity of GCS it has been common to introduce halogen substituents into the 6α- or 9α- or both 6α,9α-positions (19, 20, 23, 24). Decreased biotransformation rate (16, 28) and reduced transcortin binding (2) may explain the enhanced activity of such GCS, but increased affinity to the GCS receptor may also be a contributory factor (15, 28). The relative importance of each of these contributions has not been evaluated. The necessity of halogen substitution for reaching high topical activity is not so well documented. We, therefore, decided to study the influence of steroid nucleus fluorination on the topical and the systemic activity of different types of GCS 16α,17α-acetals. This type of GCS was preferred for two reasons (a) the topical (or local) activity of such compounds could be enhanced by changing the 16α,17α-acetal substituent (5, 26) and (b) the local biotransformation of such drugs seems to be restricted in the lung (3) or in the skin (1). The latter would secure a high GCS activity at the site of application, which might be of great importance in inhalation therapy of e.g. severe asthma.

The structure-activity investigations clearly showed that, to secure high topical

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anti-inflammatory activity, it was more important to optimize the 16α,17α-acetal substitution (26) than to introduce fluorine atoms in the 6α-, 9α- or 6α, 9α-positions. This structural change in the acetal group did not enhance, but instead tended to reduce, the systemic activity. Steroid nucleus fluorination, on the other hand, potentiated the systemic activity much more than the topical activity. Budesonide (Fig 5) reached a much higher topical/systemic ratio than the halogenated 16α,17α-acetonides as documented in rats and than 17α-ester compounds as BDP or betamethasone 17-valerate (results not shown) as studied in mice.

The markedly enhanced topical/systemic ratio of budesonide depends on a suitable combination of properties. As budesonide is a very potent GCS at the application site the molecule probably has a high affinity to the receptor. The lack of biotransformation in the skin and lung (1, 3) contributes to a high local concentration of unchanged drug in the target organ.

When budesonide was given by systemic routes its anti-inflammatory potency was not greater than its other kinds of systemic GCS activity, e.g. thymus involution (26). This shows that budesonide, like other GCS, cannot differentiate between anti-inflammatory and other kinds of GCS effects at the receptor level. A much more probable explanation for the relatively low systemic activity of budesonide is its rapid inactivation by biotransformation after absorption from the sites of deposition. In SKF-525 A treated rats, where the drug metabolizing enzymes of the liver were blocked (12), the systemic potency of budesonide was 4—5 times that of saline-treated animals. This indicates that liver biotransformation is normally a very efficient process for inactivating budesonide. In vitro studies with liver preparations have shown that budesonide is biotransformed several times more rapidly than the halogenated GCS triamcinolone acetonide and beclomethasone 17α-monopropionate (1, 22). The rapid liver biotransformation of budesonide might, at least partly, be related to its lack of halogen substituents. Steroid nucleus halogenation is reported to decrease the biotransformation rate (28) and is thought thereby to greatly enhance the systemic activity of GCS (16).

Since there is no local inactivation by biotransformation of 16α,17α-acetal GCS in lung or skin, halogen substitution would have a less strong potentiating effect on the topical anti-inflammatory, than on the systemic, activity of such com-
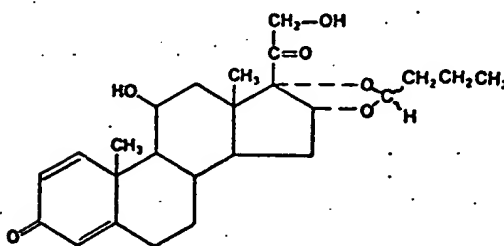

Figure 5.
Structural formula of budesonide (16α,17α-butylidenedioxy-11β, 21-dihydroxypregna-1,4-diene-3, 20-dione).

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pounds. Such a hypothesis is strongly supported by the results of the present structure-activity investigation. Halogen substitution enhanced, however, the topical anti-inflammatory potency to some extent, but this might depend on the increased intrinsic activity of such compounds (15, 28). Modification of the 16α,17α-acetal group was a more selective way to raise the topical anti-inflammatory potency as this was reached without a concomitant increase in the systemic activity. In fact, the new type of asymmetric 16α,17α-acetals tended to have a somewhat lower systemic activity than the corresponding 16α,17α-acetonides.

In conclusion, the reported structure-activity investigation has resulted in the development of budesonide, a new potent 16α,17α-acetal GCS without halogen atoms in its structure. Budesonide has demonstrated a markedly improved selectivity for glucocorticoid activity only at the site of application, which makes it highly suitable for inhalation therapy. Even if also the GCS currently used for inhalation therapy are rather selective, an improved 16α,17α-acetal GCS, such as budesonide, which retains its full activity at the site of application, might increase the possibility to effectively treat also severe asthma with GCS by inhalation only (21). Furthermore, GCS like budesonide with a reduced risk of undesired systemic effects might, thanks to the possibility of a more liberal use of GCS, also facilitate the clinical situation for many patients with asthma and rhinitis.

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